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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,375	07/29/2003	Michel Schneider	BR029-US-02	8951

7590
Bracco Research USA
305 College Road East
Princeton, NJ 08540

EXAMINER

EBRAHIM, NABILA G

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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12/29/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/630,375	Applicant(s) SCHNEIDER ET AL.	
	Examiner NABILA G. EBRAHIM	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15, 24-46 and 50-52 is/are pending in the application.
- 4a) Of the above claim(s) 1-15 and 33-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-32 and 50-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Receipt of Applicant's arguments dated 8/19/2009 is acknowledged.

Status of Claims

Claims 24-32 and 50-52 are under current examination.

Claims 16-23 and 47-49 were cancelled.

Claims 1-15 and 33-46 were withdrawn from consideration due to election/restriction requirement.

Status of Office Action: Final.

Claim Rejections - 35 USC § 112

1. In light of cancelling claim 49, the rejection of claims 49 and 51 under 35 U.S.C. 112, second paragraph, as being indefinite is hereby withdrawn.

Claim Rejections - 35 USC § 102

2. In view of amending the claims and Applicant's arguments, the rejection of claim 24, 28-32 and 50-52 under 35 U.S.C. 102(b) as being anticipated by Schneider et al. EP 0554213, is hereby withdrawn.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 24-32 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. EP 0554213 (Schneider) in view of Hugh D. Van Liew, Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, *J Appl Physiol* 82:2045-2053, 1997 (hereinafter Hugh).

Schneider teaches microbubbles that are advantageously formed from an aqueous liquid and a dry powder (microvesicle precursors) containing lamellarized freeze-dried phospholipids and stabilizers; the microbubbles are developed by agitation of this powder in admixture with the aqueous liquid carrier (page 4, lines 7+). The phospholipid is Dipalmitoylphosphatidylglycerol (example 8). Schneider explains that the vesicle suspensions, or preferably precursors thereof (precursors here mean the materials the microvesicle envelopes are made of, or the materials which, upon agitation with an aqueous carrier liquid, will generate or develop the formation of microbubbles in this liquid), can be exposed to reduced pressure to evacuate the gas to be removed and then the ambient pressure is restored with the desired gas for substitution and that this step can be repeated once or more times to ensure complete replacement of the original gas by the new one (page 4, lines 29+). Further, Schneider teaches that it is advantageous to store this dry powder under an atmosphere of a gas selected according to the invention (page 4, lines 39+). In addition, the reference discloses that it has been surprisingly found that for gases where the pressure difference $DP = P_{25} - P_{75}$ exceeds a value of about 25 - 30 Torr, the killing effect of the blood pressure on the gas-filled microvesicles is minimized (page 6, lines 20+). The gaseous species which particularly suit the invention are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like SF_6 , SeF_6 and the like (page 6, lines 38-39). Further, the reference teaches a preparation of such kind will keep indefinitely in this state and can be used at any time for diagnosis, provided it is dispersed into sterile water before injection (page 4, lines 40-42). Thus, the reference

teaches that the powder is stored solely in a container and the liquid carrier is stored in a different container which reads on instant claims 24 and 32.

Note that the amendments recited in claim 24 would not differentiate the instant claim over the prior art. The recitation that the container is sealed to produce the contrast agent renders the claim a product by process claim. The product-by-process claims are limited and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by- process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113).

Schneider did not disclose literally the pressures values recited in instant 25-27.

Hugh teaches Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, the reference discloses that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare gas microvesicles disclosed by Schneider having lowered pressure and applying Hugh's knowledge that negative pressure inside the bubble to counter the tendency for outward diffusion of the gases as disclosed by Hugh. The person of ordinary skill would be able to determine the right amount of lowered pressure used inside the bubble according to the equation disclosed by Schneider that where the pressure difference $DP = P_{25} - P_{75}$ exceeds a value of about 25 - 30 Torr.

The skilled artisan would have expectations of success to have a composition for contrast agent in an aqueous suspension containing gas-filled microvesicles useful in imaging.

Double Patenting

1. Claims 24, 28-32 and 50-52 remain rejected on the ground of nonstatutory obviousness-type double patenting as set forth in the office action dated 10/24/2008.

Response to Arguments

Applicant's arguments filed 8/19/2009 have been fully considered but they are not persuasive. Applicant argues that:

- Schneider does not teach or suggest a sealed container comprising a dried material comprising at least one film forming surfactant and a gas at lower than atmospheric pressure. The only disclosure in Schneider of use gas at reduced pressure is as an intermediate step in a process to replace a first gas with a second, desired gas, which is at ambient, not reduced pressure.

This was not found persuasive because Applicant's amendment to the claim renders the claim to a product by process claim. The product-by-process claims are limited and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by- process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113). Therefore, arguing steps done by Schneider to a sealing procedure recited in the instant claims would not be persuasive.

- The pressure difference $DP=P_{25}-P_{75}$, mentioned by the Examiner and the critical pressure, P_c , mentioned in Schneider refer to external pressures applied to suspensions of microvesicles.

This was not found persuasive because Hugh teaches that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (see page 2045, right column). Therefore, while Schneider teaches the importance of the pressure applied to the bubbles, Hugh teaches that stabilizing the bubbles is crucially dependent on the negative pressure inside the bubbles.

- The Van Liew article fails to remedy this deficiency. Like Schneider, the Van Liew article fails to teach or suggest sealed containers including contrast agent precursor compositions comprising dried materials and a gas at a pressure lower than atmospheric pressure. Indeed, Van Liew is directed to the properties of aqueous suspensions of microbubbles and does not even discuss precursor compositions used to prepare such suspensions. Thus, Van Liew cannot remedy the deficiencies of Schneider.

This was not found persuasive because Van Liew (Hugh) is relied upon as a secondary reference to obviate the lower pressure inside the microvesicles as required by instant claims. Therefore, Hugh teaches the knowledge which Schneider did not disclose.

- The phrase "negative pressure" in Van Liew does not refer to an "absolute" negative pressure (in the sense that the pressure inside the bubble is lower than the

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pressure in the surrounding medium, i.e. atmospheric pressure), but rather to a pressure which counters (i.e. having an opposite direction) the internal overpressure (with respect to the surrounding pressure) caused by surface tension at the gas-liquid interface.

To respond to Applicant's arguments, the reference teaches literally that "the reference discloses that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside". The disclosure is clear in the sense that the negative pressure inside the bubbles should be lowered than the surrounding pressure to help stabilizing the bubbles.

Double Patenting

- Like Schneider, the cited patents and applications fail to teach or suggest the claimed compositions or containers comprising a dried material and a gas at reduced pressure as required by the instant claims

To respond: as discussed supra, even if it did not teach literally that the pressure of the gas should be less than atmospheric pressure, Hugh is relied upon for teaching that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column)..

Thus the rejections are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 9:00AM - 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art
Unit 1618